

Answer 1:

Bibliographic Information

Impact of imatinib* on the pharmacokinetics and in vivo efficacy of etoposide and/or ifosfamide. Rezai, Keyvan; Lokiec, Francois; Grandjean, Isabelle; Weill, Sophie; de Cremoux, Patricia; Bordier, Vincent; Ekue, Richard; Garcia, Mickael; Poupon, Marie-France; Decaudin, Didier. Department of Pharmacology Oncology, Centre Rene Huguenin, Saint-Cloud, Fr. BMC Pharmacology (2007), 7 No pp. given. Publisher: BioMed Central Ltd., CODEN: BPMHBU ISSN: 1471-2210. <http://www.biomedcentral.com/content/pdf/1471-2210-7-13.pdf> Journal; Online Computer File written in English. CAN 148:229420 AN 2008:77247 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Background: Using a human small cell lung cancer (SCLC) xenografted in nude mice, we have previously reported enhanced tumor growth inhibition following chemotherapy in combination with imatinib (STI571). We therefore investigated the in vivo impact of imatinib on the pharmacokinetics and efficacy of chemotherapy. Methods: Two different human tumors were used: SCLC6 small cell lung cancer xenografted in nude mice, and LY-3 EBV-assocd. human B-cell lymphoma xenografted in SCID mice. Plasma, urine, and fecal concns. of etoposide (VP16) were detd. by a validated high performance liq. chromatog. method. Plasma concns. of ifosfamide were detd. by a validated gas chromatog. assay with nitrogen-phosphorus detection. Results: Slight tumor growth inhibition was induced by imatinib administered alone in one in vivo EBV-assocd. B-cell lymphomatous xenograft. In contrast, an increase of the chemotherapy-induced antitumor effect was obsd. in the lymphoma model but not in a small cell lung cancer model when mice bearing human xenografted tumors were treated concomitantly by imatinib and chemotherapy. This antitumor effect was not influenced by concomitant administration of fluconazole. The AUC0-3h (Area Under the concn.-time Curve) of etoposide was increased when mice were treated with etoposide + imatinib due to decreased fecal excretion. In contrast, imatinib did not appear to influence the urinary excretion of etoposide, and concomitant administration of the CYP3A4 inhibitor, fluconazole, with imatinib did not modify the pharmacokinetics of etoposide plus imatinib alone. Conclusions: Altogether, these results therefore justify further prospective phase I and II clin. trials with combinations of etoposide-based chemotherapy and imatinib in patients with certain cancers, such as malignant lymphoma, with careful toxicol. monitoring.

Answer 2:

Bibliographic Information

Treatment with imatinib improves drug delivery and efficacy in NSCLC xenografts. Vlahovic, G.; Ponce, A. M.; Rabbani, Z.; Salahuddin, F. K.; Zgonjanin, L.; Spasojevic, I.; Vujaskovic, Z.; Dewhirst, M. W. Department of Medicine - Oncology, Duke University Medical Center, Durham, NC, USA. British Journal of Cancer (2007), 97(6), 735-740. Publisher: Nature Publishing Group, CODEN: BJCAAI ISSN: 0007-0920. Journal written in English. CAN 148:135207 AN 2007:1017219 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Imatinib, an inhibitor of PDGF-R β and other tyrosine kinase receptors, has been shown to decrease microvessel d. and interstitial fluid pressure in solid tumors, thereby improving subsequent delivery of small mols. The purpose of this study was to test whether pretreatment with imatinib increases the efficacy of traditional chemotherapy in mice bearing non-small cell lung carcinoma xenografts, and to investigate the effects of imatinib on liposomal drug delivery. Efficacy treatment groups included (n = 9-10): saline control, imatinib alone (oral gavage, 100 mg kg⁻¹ \times 7 days), docetaxel alone (10 mg kg⁻¹ i.p. 2 \times /wk until killing), and imatinib plus docetaxel (started on day 7 of imatinib). Tumors were monitored until they reached four times the initial treatment vol. (4 \times V) or 28 days. A sep. expt. compared tumor doxorubicin concns. (using high performance liq. chromatog.) 24 h after treatment with liposomal doxorubicin alone (6 mg kg⁻¹ i.v., n = 9) or imatinib plus liposomal doxorubicin (n = 16). Imatinib plus docetaxel resulted in significantly improved antitumor efficacy (0/10 animals reached 4 \times V by 28 days) when compared to docetaxel alone (3/9 reached 4 \times V, P = 0.014) or imatinib alone (9/10 reached 4 \times V, P = 0.025). Pretreatment with imatinib also significantly increased tumor concns. of liposomal doxorubicin. Overall, these preclin. studies emphasize the potential of imatinib as an adjunct to small mol. or liposomal chemotherapy. Published online.

Answer 3:

Bibliographic Information

Imatinib mesylate reduces rituximab-induced tumor-growth inhibition in vivo on Epstein-Barr virus-associated human B-cell lymphoma. Nemati, Fariba; Mathiot, Claire; Grandjean, Isabelle; Lantz, Olivier; Bordier, Vincent; Dewulf, Sebastien; Ekue, Richard; Di Santo, James P.; Poupon, Marie-France; Decaudin, Didier. Laboratory of Pre-clinical Investigations, Institut National de la Sante et de la Recherche Medicale Unite, Paris, Fr. *Anti-Cancer Drugs* (2007), 18(9), 1029-1037. Publisher: Lippincott Williams & Wilkins, CODEN: ANTDEV ISSN: 0959-4973. Journal written in English. CAN 147:419446 AN 2007:914839 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

We have reported earlier an increase of tumor-growth inhibition following chemotherapy combined with concomitant administration of imatinib mesylate. Conversely, the combination of imatinib and rituximab has been reported in very few cases of patients and remains controversial. To explore this particular combination of targeted therapies, we therefore investigated the in-vivo impact of rituximab plus imatinib on B-cell lymphoproliferation. Combination of the tyrosine kinase inhibitor imatinib mesylate (STI571) and the anti-CD20 monoclonal antibody rituximab was evaluated on an Epstein-Barr virus-assocd. B-cell lymphoproliferative disorder xenografted into severe combined immunodeficient or Rag2 γ c (B, T and NK) mice. Using severe combined immunodeficient mice, we found that STI571 diminished the efficacy of rituximab to inhibit tumor growth in vivo. Using alymphoid Rag2 γ c mice, we showed that the effect of STI571 was not dependent on the presence of natural killer cells. In contrast, serum complement administered after STI571 treatment reversed this inhibitory effect. Finally, using nonimmunodeficient mice, we obsd. an in-vivo decrease of CD4-pos. T-cells and mature B-cell lymphocytes after imatinib administration. We found that STI571 decreased the in-vivo efficacy of rituximab via serum protein components that could influence complement-dependent cytotoxicity. In contrast, this effect was not dependent on the presence of natural killer cells.

Answer 4:

Bibliographic Information

Imatinib mesylate inhibits tumorigenicity of malignant fibrous histiocytoma cells in vivo. Irsan, Istan; Akisue, Toshihiro; Hara, Hitomi; Fujimoto, Takuya; Imabori, Masaya; Doita, Minoru; Kuroda, Ryosuke; Fujioka, Hiroyuki; Kawamoto, Teruya; Yamamoto, Tetsuji; Kurosaka, Masahiro. Department of Orthopedic Surgery, Kobe University Graduate School of Medicine, Hyogo, Japan. *Anticancer Research* (2007), 27(1A), 423-430. Publisher: International Institute of Anticancer Research, CODEN: ANTRD4 ISSN: 0250-7005. Journal written in English. CAN 146:454423 AN 2007:361448 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Malignant fibrous histiocytoma (MFH) is one of the most diffuse and aggressive tumors among soft tissue sarcomas in adults, but still poorly characterized from the mol. viewpoint. MFH cell proliferation is inhibited selectively by imatinib mesylate, a tyrosine kinase inhibitor. The expressions of platelet-derived growth factor receptors (PDGFRs) and c-Kit have been previously examd. in MFH cell lines and the inhibitory effect of imatinib mesylate on the MFH cell proliferation was tested. MFH cell lines showed various patterns of PDGFRs and c-Kit expression. Imatinib mesylate inhibited the proliferation of MFH cells that expressed PDGFRs and/or c-Kit. Four MFH cell lines were used (Nara H, Nara F, GBS-1 and TNMY1). The mRNA expression of PDGFRs and c-Kit was analyzed using RT-PCR; cell proliferation was analyzed using the MTS assay. Immunohistochem. was used to analyze the inhibitory effect of imatinib mesylate on phosphorylation of PDGFRs and c-Kit in vivo. The Nara H and TNMY1 cell lines were implanted into nude mice and tumor growth was evaluated daily by measuring the two-dimensional diams. of the tumor nodule. PDGFRs and c-Kit were expressed in Nara F, GBS-1 and TNMY1, but not in Nara H cells. Imatinib mesylate inhibited PDGFRs and c-Kit phosphorylation in TNMY1 cells affecting the tumorigenicity, in the control group (139 mm³ SD \pm 1.03) and treatment group (126.2 mm³ SD \pm 1.63) but did not affect the tumorigenicity of Nara H cells. Imatinib mesylate reduced in vivo tumor growth of MFH that express PDGFRs and c-Kit assocd. with phosphorylation suppression.

Answer 5:

Bibliographic Information

The tyrosine kinase inhibitor imatinib [STI571] induces regression of xenografted canine mast cell tumors in SCID mice.

Kobie, Keiko; Kawabata, Mariko; Hioki, Kyoji; Tanaka, Akane; Matsuda, Hiroshi; Mori, Takashi; Maruo, Kohji. Department of Veterinary Surgery, Faculty of Agriculture, Tokyo University of Agriculture and Technology, Fuchu, Tokyo, Japan. Research in Veterinary Science (2006), Volume Date 2007, 82(2), 239-241. Publisher: Elsevier Ltd., CODEN: RVTSA9 ISSN: 0034-5288. Journal written in English. CAN 146:492766 AN 2007:164368 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Canine mast cell tumors (MCTs) are the most common cutaneous tumors in the dog. They have a wide range of behavior, which can make these tumors challenging to treat. Recently, mutations in c-kit proto-oncogene have been identified in several canine MCTs. Imatinib is the first member of a new class of agents that act by inhibiting particular tyrosine kinase enzymes, including KIT which is a product of the c-kit. In this study the efficacy of imatinib to reduce or abolish canine MCT [CMC-1] using xenografted MCT in severe combined immunodeficient [SCID] mice was evaluated. Imatinib was administered at doses of 200 mg/kg and 100 mg/kg once a day for one week. The antitumor responses in SCID mice with CMC-1 xenografts following treatment with imatinib were obsd. Significant tumor regression occurred with 100 mg/kg on days 7, 10, 14 and 21, and 200 mg/kg on all days. Our results indicate that imatinib is effective against canine mast cell tumor in mouse xenograft models. Canine MCTs might be a potential target for imatinib therapy.

Answer 6:

Bibliographic Information

Evidence for PDGFRA, PDGFRB and KIT deregulation in an NSCLC patient. Negri, T.; Casieri, P.; Miselli, F.; Orsenigo, M.; Piacenza, C.; Stacchiotti, S.; Bidoli, P.; Casali, P. G.; Pierotti, M. A.; Tamborini, E.; Pilotti, S. Laboratory of Experimental Molecular Pathology, IRCCS Istituto Nazionale dei Tumori, Milan, Italy. British Journal of Cancer (2007), 96(1), 180-181. Publisher: Nature Publishing Group, CODEN: BJCAAI ISSN: 0007-0920. Journal; General Review written in English. CAN 146:518941 AN 2007:26646 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

A review. The research of Vlahovic et al. (2006) entitled "Treatment with Imatinib in NSCLC is assocd. with decrease of phosphorylated PDGFR-beta and VEGF expression, decrease in interstitial fluid pressure and improvement of oxygenation" is reviewed with commentary and refs. Vlahovic et al. provided evidence of effectiveness of Imatinib treatment in PDGFRB-overexpressing human lung adenocarcinoma xenografts grown in nude mice. In this preclin. model, the effectiveness of the drug is related to decrease in interstitial fluid pressure, decrease of phosphorylated PDGFRB and VEGF expression and improvement of oxygenation. Imatinib in adjunction to chemotherapy may also be effective in a lung adenocarcinoma made up of tumor cells expressing Imatinib-sensitive deregulated genes such as PDGFRA, PDGFRB and c-Kit in presence of EGFR and HER-2/neu amplification lacking any evidence of protein expression.

Answer 7:

Bibliographic Information

Emerging Role of Platelet-Derived Growth Factor Receptor- α Inhibition in Radioimmunotherapy of Experimental Pancreatic Cancer. Baranowska-Kortylewicz, Janina; Abe, Michio; Nearman, Jessica; Enke, Charles A. Department of Radiation Oncology, J. Bruce Henriksen Cancer Research Laboratories, University of Nebraska Medical Center, Omaha, NE, USA. Clinical Cancer Research (2007), 13(1), 299-306. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 146:266009 AN 2007:8320 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Purpose: Thus far, the therapy of pancreatic cancer remains an insurmountable challenge. Not a solitary therapeutic modality in the battery of available therapeutic options is capable to cure or, at the very least, stop the progression of this disease in any meaningful way. The purpose of reported here studies was to implement a multimodality approach to radio-immunotherapy of pancreatic cancer and, ultimately, to develop a course of therapy with the clin. value. **Exptl. Design:** Animal model was NCr-nu/nu mouse bearing s.c. xenografts of SW1990 pancreatic adenocarcinoma. Radioimmunotherapy based on 131ICC49, a TAG-72-targeting monoclonal antibody, was augmented with imatinib, a potent inhibitor of platelet-derived growth factor receptor- $\{\alpha\}$. The postulated interactions between these two modalities depended on the imatinib-induced drop in the tumor interstitial fluid pressure and the subsequent increase of 131ICC49 uptake into the tumor, resulting in improved tumor responses to radio-immunotherapy. **Results:** Biodistribution studies revealed a 50% improvement in the tumor uptake of 131ICC49 in mice treated with imatinib. Tumor development was practically arrested for .apprx.3 wk in response to the treatment composed of 131ICC49 and imatinib with tumor quadrupling time (TQ) of 40.8 days. 131ICC49 alone and imatinib alone also delayed the tumor growth to TQ of 30.2 and 31.2 days, resp. Unanticipated was the significant response of SW1990 to a brief treatment with imatinib given i.p. at 100 mg/kg b.i.d. for 3 days. Xenografts in control mice receiving injection of PBS had TQ of 23 days. **Conclusions:** The inclusion of imatinib in the radio-immunotherapy regimen is beneficial and it does not produce any overt side effects. The improved responses of pancreatic cancer xenografts to the multimodality treatment comprising radio-immunotherapy and platelet-derived growth factor receptor- $\{\alpha\}$ inhibition suggest that this approach to therapy of pancreatic cancer may also be successful in patients.

Answer 8:

Bibliographic Information

Patupilone (epothilone B, EPO906) and imatinib (STI571, Glivec) in combination display enhanced antitumour activity in vivo against experimental rat C6 glioma. O'Reilly, T.; Wartmann, M.; Maira, S.-M.; Hattenberger, M.; Vaxelaire, J.; Muller, M.; Ferretti, S.; Buchdunger, E.; Altmann, K.-H.; McSheehy, P. M. J. *Oncology Research*, Novartis Institutes for BioMedical Research, Basel, Switz. *Cancer Chemotherapy and Pharmacology* (2005), 55(4), 307-317. Publisher: Springer GmbH, CODEN: CCPHDZ ISSN: 0344-5704. Journal written in English. CAN 142:475425 AN 2005:149169 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Purpose The microtubule-stabilizing agent patupilone (epothilone B, EPO906) and the tyrosine kinase inhibitor imatinib (STI571, Glivec) which primarily inhibits Bcr-Abl, PDGF and c-Kit tyrosine kinase receptors, were combined in vivo to det. if any interaction would occur with respect to antitumor effect and tolerability using rat C6 glioma xenografted into nude mice. **Methods** Patupilone and imatinib were administered alone or in combination at suboptimal doses. Imatinib treatment (orally once daily) was initiated 4 days after s.c. injection of rat C6 glioma cells into athymic nude mice and patupilone administration (i.v. once per wk) was started 3 or 4 days after imatinib treatment. **Results** As a single agent, imatinib was inactive in the regimens selected (100 mg/kg: T/C 86% and 116%; 200 mg/kg: T/C 68% and 84%; two independent expts.), but well tolerated (gain in body wt. and no mortalities). Patupilone weekly monotherapy demonstrated dose-dependent antitumor effects (1 mg/kg: T/C 67% and 70%; 2 mg/kg: T/C 32% and 63%; 4 mg/kg: T/C 3% and 46%). As expected, dose-dependent body wt. losses occurred (final body wt. changes at 1 mg/kg were -7% and -3%; at 2 mg/kg were -23% and -13%; and at 4 mg/kg were -33% and -15%). Combining 2 mg/kg patupilone and 200 mg/kg per day imatinib in one expt. produced a non-statistically significant trend for an improved antitumor effect over patupilone alone (combination, T/C 9%), while in the second expt., enhancement was seen with the combination and reached statistical significance vs. patupilone alone (combination, T/C 22%; $P=0.008$). Redn. of the imatinib dose to 100 mg/kg per day resulted in no enhancement of antitumor activity in combination with 2 mg/kg patupilone. Redn. of the patupilone dose to 1 mg/kg resulted in a reduced antitumor effect, and only a trend for synergy with either imatinib dose (combination, T/C 46% and 40%). Pooling the data from the two expts.

confirmed a significant synergy for the combination of 2 mg/kg patupilone and 200 mg/kg per day imatinib ($P=0.032$), and a trend for synergy at the 1 mg/kg patupilone dose. Redn. in the imatinib dose to 100 mg/kg per day resulted only in additivity with either dose of patupilone. Body wt. losses were dominated by the effect of patupilone, since no greater body wt. loss was obsd. in the combination groups. **Conclusion** Combining patupilone with high-dose imatinib produced an increased antitumor effect without affecting the tolerability of treatment in a relatively chemoresistant rat C6 glioma model. Such results indicate that further evaluation is warranted, in particular to elucidate possible mechanisms of combined action.

Answer 9:

Bibliographic Information

Imatinib mesylate inhibits platelet-derived growth factor activity and increases chemosensitivity in feline vaccine-associated sarcoma. Katayama, Rieko; Huelsmeyer, Michael K.; Marr, Amanda K.; Kurzman, Ilene D.; Thamm, Douglas H.; Vail, David M. Department of Medical Sciences, School of Veterinary Medicine, University of Wisconsin-Madison, Madison, WI, USA. Cancer Chemotherapy and Pharmacology (2004), 54(1), 25-33. Publisher: Springer-Verlag, CODEN: CCPHDZ ISSN: 0344-5704. Journal written in English. CAN 142:16318 AN 2004:450175 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Feline vaccine-assocd. sarcoma (VAS) is a biol. aggressive soft-tissue sarcoma that can develop at sites where inactivated feline vaccines have been administered. We showed that platelet-derived growth factor (PDGF) and its receptor (PDGFR) play a role in the growth of VAS cells. The presence of PDGFR- β was confirmed in each of five VAS cell lines evaluated, one non-vaccine-assocd. feline fibrosarcoma (FSA) cell line and a feline fibroblast-derived cell line. The PDGF/PDGFR signaling pathway was inhibited in the VAS cell lines and the FSA cell line using the tyrosine kinase inhibitor imatinib mesylate (formerly called STI-571). Imatinib inhibited PDGF-BB-induced autophosphorylation of PDGFR in VAS cells and feline FSA cells in vitro in a dose-dependent manner. Imatinib also significantly inhibited growth of feline VAS tumors in a murine xenograft model. Imatinib reversed the protective effect of PDGF-BB on growth inhibition by doxorubicin and carboplatin. PDGF-BB protected VAS cells from serum starvation and doxorubicin-induced apoptosis but not carboplatin-induced apoptosis, and imatinib eliminated this protection. These observations suggest that imatinib inhibits PDGFR tyrosine kinase activity in feline soft tissue sarcomas in vitro and inhibits tumor growth in a xenograft model.

Answer 10:

Bibliographic Information

The third-generation bisphosphonate zoledronate synergistically augments the anti-Ph+ leukemia activity of imatinib mesylate. Kimura, Shinya; Kuroda, Junya; Maekawa, Taira. School of Medicine, Affiliated Hospital, Kyoto University, Japan. Ensho, Saisei (2004), 24(2), 113-117. Publisher: Nippon Ensho-Saisei Igakkai, CODEN: ENSHCC ISSN: 1346-8022. Journal written in Japanese. CAN 141:167358 AN 2004:450068 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Imatinib mesylate, a competitive inhibitor for of ABL tyrosine kinase, is highly active against Philadelphia-pos. (Ph+) chronic myelocytic leukemia. However, recent studies demonstrated the existence of primary and/or acquired imatinib-resistant Ph+ clones those would affect the treatment outcome. For the development of the strategies those strengthen the effect of imatinib, we selected Ras related proteins as an alternative mol. target, because these proteins enhance the oncogenetic property of BCR/ABL as downstream signaling effector. Based on the previous findings showing the inhibitory effect for Ras related proteins of the third-generation bisphosphonate, zoledronate (ZOL), we examd. its anti-leukemic potencies and the combination effect with imatinib against Ph+ leukemia both in vivo and in vitro. ZOL showed a time- and concn.-dependent antiproliferative effect in all examd. leukemic cell lines by inducing apoptosis. During the apoptotic execution, ZOL inactivated Ras related proteins via prevention of the posttranslational prenylation. The combination of imatinib and ZOL showed the synergistic anti-proliferative effects against Ph, leukemic cell lines in vitro, and, intriguingly, this combination could prolong the survival of mice xenografted with Ph, BV173 cell line in comparison with mice treated with imatinib or ZOL alone. These suggest that ZOL is a potent anti-leukemic agent that synergistically augments the effect of imatinib.

Answer 11:

Bibliographic Information

Imatinib mesylate efficiently achieves therapeutic intratumor concentrations in vivo but has limited activity in a xenograft model of small cell lung cancer. Wolff, Nicholas C.; Randle, Dwight E.; Egorin, Merrill J.; Minna, John D.; Ilaria, Robert L., Jr.

Hammon Center for Therapeutic Oncology Research, University of Texas Southwestern Medical Center, Dallas, TX, USA. Clinical Cancer Research (2004), 10(10), 3528-3534. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 142:16302 AN 2004:425244 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Despite recent advances in cancer therapy, long-term survival in small cell lung cancer (SCLC) remains uncommon, underscoring the need for novel therapeutic approaches. Previous studies have identified constitutive expression of the receptor tyrosine kinase, c-Kit, and its ligand, stem cell factor, in a substantial proportion of SCLC specimens. The purpose of this study was to det. whether imatinib mesylate, an inhibitor of c-Kit, could achieve therapeutic concns. in tumors and in brain (a frequent site of SCLC metastasis) and interfere with SCLC tumor growth in vivo. Human SCLC tumor cell lines with constitutive c-kit expression and tyrosine phosphorylation (NCI-H209, NCI-H526, and NCI-H1607) were used to establish SCLC tumor xenografts in NCr nude (nu/nu)-immunodeficient mice. SCLC tumor-bearing mice were randomly assigned to imatinib or control (water) administered twice a day by oral gavage. Imatinib concns. in plasma, brain, and tumor were quantitated and correlated with tumor response. Therapeutic concns. of imatinib were achieved in plasma and tumor xenografts but not in the brain. Imatinib blocked the constitutive activation of c-kit in SCLC tumor cell lines in vitro but had a negligible effect on SCLC xenograft growth in vivo. Orally administered imatinib rapidly reaches therapeutic concns. in SCLC xenografts, suggesting the feasibility of combining imatinib with other novel or traditional chemotherapeutic agents in SCLC or other solid tumors. The c-Kit signaling pathway does not appear to play a crit. role in SCLC proliferation and viability in vivo, however, suggesting that imatinib is unlikely to be effective as monotherapy for SCLC.

Answer 12:

Bibliographic Information

Effect of imatinib mesylate on neuroblastoma tumorigenesis and vascular endothelial growth factor expression. Beppu, Kiichiro; Jaboine, Jerry; Merchant, Melinda S.; Mackall, Crystal L.; Thiele, Carol J. Pediatric Oncology Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA. Journal of the National Cancer Institute (2004), 96(1), 46-55. Publisher: Oxford University Press, CODEN: JNCIEQ ISSN: 0027-8874. Journal written in English. CAN 141:33408 AN 2004:27280 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Alternative treatment options are needed for advanced neuroblastoma patients because their prognosis remains poor after intensive chemotherapy. Neuroblastoma cells express platelet-derived growth factor (PDGF), stem cell factor (SCF), and vascular endothelial growth factor (VEGF) and their resp. receptors, PDGFR, c-Kit, and Flk-1. We therefore evaluated the effects of imatinib mesylate (imatinib), a selective inhibitor of the tyrosine kinase activities of c-Kit and PDGFR, on the growth of neuroblastoma cells in vivo and in vitro. We tested seven human neuroblastoma cell lines for their sensitivity to imatinib. Cell viability was assessed by trypan blue dye exclusion. Apoptosis was evaluated by nuclear staining, flow cytometry, and western blotting. Protein assays included immunopptn., western blotting, enzyme-linked immunosorbent assays, and immunohistochem. mRNA expression was assessed by northern blotting. We used a xenograft model in SCID mice (10 mice per group) to evaluate the effects of imatinib oral therapy (50 or 100 mg/kg every 12 h for 14 days) on neuroblastoma tumor growth. All statistical tests were two-sided. All seven neuroblastoma cell lines treated with imatinib displayed concn.-dependent decreases in cell viability, which coincided with an induction of apoptosis, and with ligand-stimulated phosphorylation of c-Kit and PDGFR. The imatinib concns. that caused 50% inhibition of growth and 50% inhibition of ligand-induced phosphorylation of these receptors were 9-13 μ M and 0.1-0.5 μ M, resp. Expression of VEGF, but not phosphorylation of Flk-1, its receptor, was reduced in neuroblastoma cells treated with imatinib at 10 μ M or higher. Mice treated with imatinib at 50 mg/kg or 100 mg/kg had statistically significantly smaller tumors than control mice treated with vehicle (mean tumor vol. in mice treated with imatinib at 50 mg/kg = 1546 mm³, in control mice = 2954 mm³; difference = 1408 mm³, 95% confidence interval [CI] = 657 to 2159 mm³; P<.001; mean tumor vol.

in mice treated with imatinib at 100 mg/kg = 463 mm³; difference = 2491 mm³, 95% CI = 1740 to 3242 mm³; P<.001). Imatinib inhibited the growth of neuroblastoma cells in vitro and in vivo. This inhibition was assocd. with suppression of PDGFR and c-Kit phosphorylation and inhibition of VEGF expression.

Answer 13:

Bibliographic Information

Potential use of imatinib in Ewing's sarcoma: evidence for in vitro and in vivo activity. Merchant, Melinda S.; Woo, Chan-Wook; Mackall, Crystal L.; Thiele, Carol J. Pediatric Oncology Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA. Journal of the National Cancer Institute (2002), 94(22), 1673-1679. Publisher: Oxford University Press, CODEN: JNCIEQ ISSN: 0027-8874. Journal written in English. CAN 139:78602 AN 2002:973981 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Ewing's sarcoma cells express c-kit, a receptor tyrosine kinase, and its ligand, stem cell factor (SCF), creating a potential autocrine loop that may promote tumor survival. We thus examd. whether the specific tyrosine kinase inhibitor imatinib mesylate (hereafter imatinib; formerly ST1571) could inhibit the proliferation of Ewing's sarcoma cells in vitro and in vivo. The effect of imatinib on c-kit expression and phosphorylation in Ewing's sarcoma cells was examd. by immunoblotting. The effect of imatinib on cell growth and apoptosis was examd. with an MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide] assay and with a morphol. test and Annexin V staining, resp. The effect of imatinib oral therapy (every 12 h for 5-7 days) on primary tumor growth was assessed in Ewing's sarcoma xenografts in SCID/bg mice (5 or 10 mice per group). All Ewing's sarcoma cell lines tested were sensitive to imatinib-mediated apoptosis with a concn. inhibiting growth by 50% (IC50) of 10-12 μ M. Imatinib inhibited SCF-mediated c-kit phosphorylation (IC50 = 0.1-0.5 μ M). In the xenograft model, imatinib treatment resulted in the regression or control of primary Ewing's sarcomas. After 6 days of treatment, the mean lower extremity vol. including xenograft tumor was 3744 mm³ (95 % confidence interval [CI] = 3050 to 4437 mm³), 1442 mm³ (95% CI = 931 to 1758 mm³), and 346 mm³ (95 % CI = 131 to 622 mm³) in mice treated with carrier alone or with imatinib at 50 mg/kg or at 100 mg/kg, resp. Imatinib interferes with growth of all Ewing's sarcoma cell lines tested in vitro and in vivo. Targeted inhibition of tyrosine kinase-dependent autocrine loops, therefore, may be a viable therapeutic strategy for Ewing's sarcoma.

Answer 14:

Bibliographic Information

Impact of imatinib on the pharmacokinetics and in vivo efficacy of etoposide and/or ifosfamide. Rezai Keyvan; Lokiec Francois; Grandjean Isabelle; Weill Sophie; de Cremoux Patricia; Bordier Vincent; Ekue Richard; Garcia Mickael; Poupon Marie-France; Decaudin Didier Department of Clinical Hematology, Institut Curie, Paris, France. k.rezai@stcloud-huguenin.org BMC pharmacology (2007), 7 13. Journal code: 100967806. E-ISSN:1471-2210. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 17963518 AN 2008014230 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

BACKGROUND: Using a human small cell lung cancer (SCLC) xenografted in nude mice, we have previously reported enhanced tumor growth inhibition following chemotherapy in combination with imatinib (STI571). We therefore investigated the in vivo impact of imatinib on the pharmacokinetics and efficacy of chemotherapy. **METHODS:** Two different human tumors were used: SCLC6 small cell lung cancer xenografted in nude mice, and LY-3 EBV-associated human B-cell lymphoma xenografted in SCID mice. Plasma, urine, and fecal concentrations of etoposide (VP16) were determined by a validated high performance liquid chromatography method. Plasma concentrations of ifosfamidewere determined by a validated gas chromatography assay with nitrogen-phosphorus detection. **RESULTS:** Slight tumor growth inhibition was induced by imatinib administered alone in one in vivo EBV-associated B-cell lymphomatous xenograft. In contrast, an increase of the chemotherapy-induced antitumor effect was observed in the lymphoma model but not in a small cell lung cancer model when mice bearing human xenografted tumors were treated concomitantly by imatinib and chemotherapy. This antitumor effect was not influenced by concomitant administration of fluconazole. The AUC_{0-3 h} (Area Under the concentration-time Curve) of etoposide was increased when mice were treated with etoposide + imatinib due to decreased fecal excretion. In contrast, imatinib did not appear to influence the urinary excretion of etoposide, and concomitant administration of the CYP3A4 inhibitor, fluconazole, with imatinib did not modify the pharmacokinetics of etoposide plus

imatinib alone. **CONCLUSION:** Altogether, these results therefore justify further prospective phase I and II clinical trials with combinations of etoposide-based chemotherapy and imatinib in patients with certain cancers, such as malignant lymphoma, with careful toxicologic monitoring.

Answer 15:

Bibliographic Information

The tyrosine kinase inhibitor imatinib [STI571] induces regression of xenografted canine mast cell tumors in SCID mice. Kobie Keiko; Kawabata Mariko; Hioki Kyoji; Tanaka Akane; Matsuda Hiroshi; Mori Takashi; Maruo Kohji
Department of Veterinary Surgery, Faculty of Agriculture, Tokyo University of Agriculture and Technology, 3-5-8 Saiwai, Fuchu, Tokyo 183-8509, Japan
Research in veterinary science (2007), 82(2), 239-41. Journal code: 0401300.
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Abstract

Canine mast cell tumors (MCTs) are the most common cutaneous tumors in the dog. They have a wide range of behaviour, which can make these tumors challenging to treat. Recently, mutations in c-kit proto-oncogene have been identified in several canine MCTs. Imatinib is the first member of a new class of agents that act by inhibiting particular tyrosin kinase enzymes, including KIT which is a product of the c-kit. In this study the efficacy of imatinib to reduce or abolish canine MCT [CMC-1] using xenografted MCT in severe combined immunodeficient [SCID] mice was evaluated. Imatinib was administered at doses of 200mg/kg and 100mg/kg once a day for one week. The antitumor responses in SCID mice with CMC-1 xenografts following treatment with imatinib were observed. Significant tumor regression occurred with 100mg/kg on days 7, 10, 14 and 21, and 200mg/kg on all days. Our results indicate that imatinib is effective against canine mast cell tumor in mouse xenograft models. Canine MCTs might be a potential target for imatinib therapy.

Answer 16:

Bibliographic Information

Dasatinib: BMS 354825. Anonymous
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Abstract

Dasatinib [BMS 354825] is an orally active, small molecule, dual inhibitor of both SRC and ABL kinases that is under development with Bristol-Myers Squibb for the treatment of patients with chronic myelogenous leukaemia (CML) and imatinib-acquired resistance/intolerance. While imatinib remains a frontline therapy for CML, patients with advanced disease frequently develop resistance to imatinib therapy through multiple mechanisms. These mechanisms include insufficient potency at therapeutic doses, activation of alternate oncogenic pathways, and overexpression of the multidrug-resistant gene. One of the possible causes of imatinib-acquired resistance is associated with increased expression of the SRC-related kinase Lyn and loss of BCR-ABL dependence arising from sequence mutations. In December 2005, Bristol-Myers Squibb announced that it has completed the rolling NDA submission to the US FDA for dasatinib in the treatment of CML in chronic, accelerated or blast phases, as well as Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukaemia (ALL) in patients with resistance or intolerance to prior treatment. At the Bristol-Myers Squibb R&D Day in May 2005, the company stated that it plans to evaluate dasatinib in solid tumours. In vitro assays, dasatinib induced apoptosis and had potent activity in the imatinib-resistant tumour cells lines and CML patient specimens. It effectively inhibited the proliferation of cells expressing nearly all imatinib-resistant isoforms. In vivo, dasatinib has shown efficacy, with no apparent toxicity, when administered orally in SCID mice with xenografts of

imatinib-sensitive and resistant human CML cells lines. Dasatinib is also undergoing preclinical evaluation for its potential as a therapy against multiple myeloma. Bristol-Myers Squibb has a composition-of-matter patent covering this research approach that will expire in 2020.